IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln. No. : 09/806,370 Confirmation No.: 8568

Appellant : Holmes et al.

Filed : October 3, 2001

TC/A.U. : 1645

Examiner : V. Portner

Docket No. : 33,383-00

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P.O. Box 1450
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BRIEF ON APPEAL

Sir:

This Appeal Brief is timely filed. A Notice of Appeal was filed by facsimile at the US Patent and Trademark Office on August 24, 2006. The appeal is from the Office Action dated May 25, 2006 and made final, which rejected pending claims 1-11, 13-17, 28-37, and 39-44.

The fee of $500.00 for filing this Appeal Brief is attached hereto. The Director is hereby authorized to charge any deficiency in any fees due with the filing of this paper or during the pendency of this application, or credit any overpayment in any fees to our Deposit Account Number 08-3040.

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I. Real party in interest

The real parties in interest are Appellants' assignees:

Wyeth Holdings Corporation located at Five Giralda Farms, Madison, New Jersey, 07940 (Wyeth Holdings Corporation is the successor-in-interest to originally-named assignee, American Cyanamid Company); and

The United States of America as represented by the Uniformed Services University of Health Sciences located at 4301 Jones Bridge Road, F. Edward Hebert School of Medicine, Bethesda, Maryland, 20814-4799.

II. Related appeals and interferences

None.

III. Status of claims

The pending claims are 1-11, 13-17, 28-37, and 39-44. Claims 1-11, 13-17, 28-37, and 39-44 stand rejected. Claims 3, 29, and 44 stand objected. Claim 28 was indicated to be allowable if (i) rewritten in independent form by including all of the features of the base claim and any intervening claims and (ii) the 35 USC § 112, second paragraph rejection as applied to this claim was overcome. Claims 3 and 44 were indicated to be in condition for allowance if the 35 USC § 112, second paragraph rejection as applied to these claims was overcome. Claims 12, 18-27, and 38 have been canceled. Claims 17, 43, and 44 are linking claims.

Claims 1-11, 13-17, 28-37, and 39-44 are the subject of this appeal.

IV. Status of amendments

The Office Action, made final, dated May 24, 2006, included an objection directed to the amendment to the specification filed July 12, 2004.[1] The specification is objected to under the provision of 35 USC § 132(a) because the amendment allegedly introduced new matter into the disclosure. The Examiner asserted that the added material, i.e., SEQ ID NO: 1, was improperly incorporated into the specification from International Patent Application Publication No. WO 93/13202 due to an asserted technical error in the accompanying declaration.[2] The Examiner required cancellation of that amendment or correction and refiling of the accompanying declaration.

Because this objection is to an amendment to the specification, not the claims, it is not believed to be subject to review upon appeal.

Appellants have filed on October 23, 2006 prior to the filing of this Appeal Brief, an Amendment under 37 CFR § 41.33, cancelling the prior introduction of SEQ ID NO: 1 into the specification, thereby eliminating the basis for the new matter rejection.

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[1] The original declaration was filed with the July 12, 2004 amendment. Following the Non-Final Action dated October 1, 2004, the Amendment filed on December 23, 2004, the prior Appeal filed June 29, 2005, and the prior Appeal Brief filed August 29, 2005, the Non-Final Rejection following the withdrawal from Appeal, dated November 14, 2005 required a newly filed declaration, which Appellants filed with the Amendment filed February 15, 2006. The refiled declaration recited the current rule 37 CFR §1.57(f), which encoded the practice in effect for such declarations at the time of filing, which rule was not enacted until after the filing date. The objection advanced in the non-final Office Action, made final, of May 24, 2006, objects to the reference in the declaration to the aforementioned rule.

[2] Page 3, point 8, paragraph 2 of the Office Action dated May 25, 2006.

V. Summary of claimed subject matter

Appellants' invention as presented in claim 1 is drawn to an antigenic composition that includes at least one antigen from a pathogenic organism selected from among a bacterium, a virus, a fungus and a parasite (page 9, lines 20-25 and original claim 1). The composition also includes an effective adjuvanting amount of a mutant cholera holotoxin (page 9, line 25-26 and original claim 1). The mutant holotoxin has reduced toxicity compared to a wild-type cholera holotoxin (page 9, lines 26-27 and original claim 1) and has an amino acid (other than aspartic acid (Asp)) which replaces the deleted glutamic acid (Glu) which naturally occurs at position 29 of the mature A subunit of the wild-type cholera holotoxin (page 9, lines 28-30 and original claim 1). The mutant holotoxin enhances the immune response in a vertebrate host to the antigen (page 9, lines 20-22).

Appellants' invention as presented in claim 3 is drawn to an antigenic composition that includes at least one antigen from a pathogenic organism selected from among a bacterium, a virus, a fungus and a parasite (page 9, lines 20-25 and original claim 1). The composition also includes an effective adjuvanting amount of a mutant cholera holotoxin (page 9, line 25-26 and original claim 1). The mutant holotoxin has reduced toxicity compared to a wild-type cholera holotoxin (page 9, lines 26-27 and original claim 1) and has a histidine which replaces the Glu which naturally occurs at position 29 of the A subunit of the wild-type cholera holotoxin (page 9, lines 30-31 and original claim 3). The mutant holotoxin enhances the immune response in a vertebrate host to the antigen (page 9, lines 20-22).

The invention as presented in claim 43 is drawn to a method for preparing an antigenic composition (page 4, lines 5-17) comprising combining at least one antigen from a pathogenic organism selected from among a bacterium, a virus, a fungus and a parasite and an effective adjuvanting amount of a mutant cholera holotoxin (page 9, line 25-26 and original claim 1). The mutant holotoxin has reduced toxicity compared to a wild-type cholera holotoxin (page 9, lines 26-27 and original claim 1)

and has an amino acid (other than aspartic acid (Asp)) which replaces the Glu which naturally occurs at position 29 of the A subunit of the wild-type cholera holotoxin (page 9, lines 28-30 and original claim 1). The mutant holotoxin enhances the immune response in a vertebrate host to the antigen (page 9, lines 20-22).

VI. Grounds of rejection to be reviewed on appeal

The issues on appeal are the following:

(a) whether the examiner's rejection of claims 1-11, 13-17, 28-37, and 39-44 under the provision of 35 USC § 112, second paragraph as allegedly failing to particularly point out and distinctly claim the subject matter should be reversed;

(b) whether the examiner's rejection of claims 1-2, 4, 6-8, 11, 13-17, 28, 30, 32-34, 37, and 39-43 under the provision of 35 USC § 102(b) over Rappuoli et al., International Patent Publication No. WO 95/17211 (hereinafter Rappuoli) as allegedly evidenced by Zhang et al., J. Mol. Biol., 251: 564, 1994 (hereinafter Zhang) should be reversed; and

(c) whether the examiner's rejection of claims 1, 2, and 13 under the provision of 35 USC § 102(b) over Glineur et al., Infection and Immunity, 62(10):4176, 1994 (hereinafter Glineur) should be reversed.

VII. Argument

Appellants note that this is the second Appeal and second Appeal Brief filed in this application in response to the 35 USC §102(b) rejections identified in paragraphs (b) and (c) below.[3] The following arguments address the 35 USC §112, second paragraph, rejection of the claims in paragraph (a) and substantially reiterate the arguments made previously to address the 35 USC §102(b) rejections.

(a) *Claims 1-11, 13-17, 28-37, and 39-44 are rejected under 35 USC § 112, second paragraph as allegedly failing to particularly point out and distinctly claim the subject matter.*

The points raised by the examiner under this rejection include that functional limitations do not define the overall structure of the claimed mutant cholera toxin (OA 5/25/06, para. 10, pg 4); that what is now claimed is a mutant CT which does not have either Glu or Asp at a corresponding position of the native wt cholera holotoxin, position 29; but how many mutations or where or what the mutations are, are not clearly nor distinctly claimed; that there is no upper limit to the number or type of mutations that can be introduced (OA 5/25/06, para. 12, pg. 4); that the specification produced mutant CT that evidenced mutations that were not defined by any specific amino acid sequence (chimeric holotoxin, combination of amino acids from two strains (OA 5/25/06, para. 14, pg. 4-5); that process claim limitations do not define a composition that comprises any specific number of mutations, any may be produced by any other process that results in a holotoxin that does not comprise a Glu or Asp at position 29, but has adjuvanting activity (OA 5/25/06, para. 16, pg. 5).

Appellants respectfully request reconsideration and withdrawal of these rejections in view of following remarks.

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[3] The first Notice of Appeal requesting appellate review of the rejections (b) and (c) was filed on June 29, 2005. Following the filing of the first Appeal Brief on August 29, 2005, the Examiner withdrew the application from appeal to issue a new Office Action. That new non-final Office Action, dated November 14, 2005, raised the pending 35 USC §112, second paragraph, rejection of the claims. These rejections were addressed in the Response filed on Feb. 15, 2006, and finally rejected in the Office Action, made final, and dated May 24, 2006. This is the second Appeal in a prosecution (including an RCE) that has previously involved six rejections and an Advisory Action.

Appellants' invention is drawn to an antigenic composition including (a) at least one antigen from a pathogenic organism selected from among a bacterium, a virus, a fungus and a parasite; and (b) an effective adjuvanting amount of a mutant cholera holotoxin (CT). The Examiner's rejections under this section are based upon the portions of Appellants' independent claims that define the mutant CT, namely, the language of claims 1 and 43, para. (b):

> "...an effective adjuvanting amount of a mutant cholera holotoxin, wherein the mutant holotoxin has reduced toxicity compared to a wild-type cholera holotoxin, and has an amino acid which replaces the deleted glutamic acid which naturally occurs at position 29 of the mature A subunit of the wild-type cholera holotoxin, wherein said amino acid is other than aspartic acid, and wherein said mutant holotoxin enhances the immune response in a vertebrate host to said antigen."

and claim 3, para. (b):

> "...an effective adjuvanting amount of a mutant cholera holotoxin, wherein the mutant holotoxin has reduced toxicity compared to wild-type cholera holotoxin, and has a histidine which replaces the glutamic acid which naturally occurs at position 29 of the A subunit of the wild-type cholera holotoxin and wherein said mutant holotoxin enhances the immune response in a vertebrate host to said antigen."

Appellants' Claims have an Unambiguous Meaning

The plain meaning of Appellants' claim language defines a mutant CT that must have certain structural characteristics **and** certain functional characteristics. The structural requirements are that the mutant cholera holotoxin of the claims (1) must be a cholera holotoxin; and (2) must have an amino acid which replaces the deleted Glu which naturally occurs at position 29 of the mature A subunit of the wild-type (wt) cholera holotoxin, wherein said amino acid is other than Asp. The functional requirements are that the mutant cholera holotoxin (3) must have reduced toxicity compared to wt CT; and (4) must enhance the immune response in a vertebrate host to said antigen.

Appellants maintain that this language in the pending claims fully satisfies all provisions of 35 USC § 112, second paragraph[4] in view of the description provided in the specification and the knowledge extant in the art at the time of filing. Further both the patent applicant, as well as one of skill in the art, are permitted to use the originally filed specification to define the terms used in the claims.

It is only through a tortured and artificial misinterpretation of the plain meaning of Appellants' claims that the Examiner can arrive at the pending grounds for rejection. Appellants respectfully submit that their claims have an unambiguous meaning and, therefore, the Examiner's grounds for rejection under §112, second paragraph, are baseless.

The term "cholera holotoxin" is clear

Prior to the filing of the present application, one of skill in the art was readily able to clearly identify a cholera holotoxin.[5] What structure defines a cholera holotoxin is clear from the known wild-type and mutant CT structures that were extant in the art from well before the priority date of this application. Mekalanos *et al*, **1983** *Nature*, 306:551-557 (Exhibit A) is the standard reference in the art for the well-known sequence of wild-type cholera toxin and its subunits.[6] Similarly, International Patent Application Publication No. WO 93/13202 (Exhibit B), which was cited in the specification, also referenced the Mekalanos sequence. Additional

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[4] "The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention."

[5] Case law is clear in that "there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure" Falkner et al., v. Inglis et al, 448 F.3d 1357, 1366, 79 USPQ 2d 1001, 1007 (Fed. Cir. 2006), *reh and reh en banc denied* (Aug. 24, 2006). While the present rejection was explicitly not made under §112 first paragraph, it would appear that the reasoning would be similar that if a sequence is known to those of skill in the art, it need not be repeated in the specification for definiteness purposes as well.

[6] See, the "Bibliography entry 1" on page 2, lines 3-4 and the first citation on page 114, labeled "Bibliography" in the Appellants' specification.

such CT sequences are also publicly available in the NCBI database, as submitted by the authors of the above-noted publication.

Because the structure of cholera toxins and their sequences were clear to one of skill in the art as of the filing date of this invention, further claim language defining the structure of a CT should not be a requirement for a claim to a mutant of a known toxin to be clear. Thus, there is no need for insertion of additional description of the variety of known CT sequences of one or more specific wild-type holotoxin or mutant CT or the size of the claimed mutant CTs into the claim to clarify the plain meaning thereof.

The phrase "an amino acid which replaces the deleted Glu which naturally occurs at position 29 of the mature A subunit of the wt cholera holotoxin, wherein said amino acid is other than Asp" is clear.

As recited in Claims 1 and 43, the mutant cholera holotoxin is a cholera holotoxin having an amino acid which replaces the deleted glutamic acid (Glu) which naturally occurs at position 29 of the mature A subunit (CT-A) of the wild-type cholera holotoxin. That amino acid is other than aspartic acid (Asp). Claim 3 clearly names the amino acid used as the replacement as His.

The reference to the wt amino acid position 29 is clear to one of skill in the art based on knowledge of the wild-type CT sequences available in the art prior to the filing date. In publications throughout the art, a reference to position 29 of wild-type cholera holotoxin subunit A is understood by those of skill in the art to mean the Glu at position 29 in the well-known sequence of subunit A cited in Mekalanos.[7]

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[7] Note that in a variety of publications, the same convention for identifying amino acid positions of cholera toxin subunit A is used, i.e., by identifying the amino acid by position number with reference to the Mekalanos publication. See, e.g., International Patent Publication Nos. WO 97/02348 (EXHIBIT C) and WO 97/29771 (EXHIBIT D) and background references cited therein; and Vadheim K.L, et al, 1994 Microb. Pathog., 17(5):339-46 (EXHIBIT E).

While all mature CT subunit A polypeptides are not identical in amino acid length, all known wild-type CT subunit A polypeptides to Appellants' knowledge have as the 29th amino acid of the mature polypeptide (*i.e.*, after removal of the signal peptide), a Glu residue. This can be readily observed by a simple alignment of the sequences. In view therefore, one of skill in the art would readily understand the claim language's reference to the "glutamic acid which naturally occurs at position 29 of the mature A subunit of the wild-type cholera holotoxin". Based on knowledge of those of ordinary skill in the art, known published CT A subunit variants at the time of filing of this application, and the teachings of Appellants' specification, one would readily understand the meaning of the naturally occurring Glu at position 29 in the A subunit of any of the known wild-type cholera holotoxin variants. Such a task is plainly well within the skill of one of ordinary skill in the art.

The pending claim language is equally definite in the recitation that the mutant cholera holotoxin contains an amino acid (other than Asp) that **replaces** the naturally-occurring Glu that occurs at wild-type cholera holotoxin subunit A position 29. Both the ordinary meaning of Appellants' claim language and the specification support that phrase when utilized to describe ***the claimed subject*** matter. The specification, including the examples, explicitly teaches that the Glu is removed and replaced by another amino acid. For instance, Example 1 specifically describes that the Glu at position 29 is replaced with a His.

The cholera toxin subunit A cannot therefore be interpreted as a CT subunit A in which the Glu29 is shifted to another position in the CT subunit by virtue of an unreplaced deletion mutant elsewhere in the mutant CT. Such an interpretation is directly contrary to the plain meaning of the claims. For example, the specification of the present application does ***not*** explicitly or inherently teach, nor does the plain meaning of the claim language imply, that replacing Glu29 with another amino acid includes the arbitrary deletion of any of the amino acids at positions 1-28, thereby resulting in a shift of amino acids to provide an amino acid other than Glu or Asp at

position 29, with the original Glu at position 29 now occupying another position in the mutant cholera holotoxin subunit A. In fact, such a teaching would be contrary to the clearly intended definition of the terms "replacing" and "deleted" in the claims. Such plain meaning in both claim language and supported by the specification does not permit an alternate interpretation that the Glu remains in the mutant CT and is merely shifted to another position.

The pending claims also recite that the Glu at position 29 is replaced with an amino acid *other than aspartic acid.* There is nothing unclear about this recitation. Simply, the amino acid that replaces the deleted Glu29 must be a known amino acid other than Glu or Asp. One of even rudimentary skill in science would understand the plain meaning of this phrase. Again, the second paragraph of § 112 requires that the specification particularly points out and distinctly claims the invention, for which it clearly does. It is not required that the claims or the specification specifically recite the names of the amino acids other than Asp, which can be used to replace the Glu at position 29. The claim language again is clear on this issue.

As is well understood by those of skill in the art, claims "...must be read in view of the specification, of which they are a part".[8] "It is therefore entirely appropriate...to rely heavily on the written description for guidance as to the meaning of the claims".[9] As noted herein, the specification including the examples clearly supports Appellants' interpretation of the claims.

Therefore, the claim language in view of the specification and the known art is clear as to both of the structural components of the claims, i.e., the specific point of mutation and the overall structure of the claimed CT protein.

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[8] Markman v. Westview Instruments, Inc., 52 F.3d 967, 979, 34 USPQ 2d 1321, 1329 (Fed. Cir. 1995), *aff'd*, 517 U.S. 370, 38 USPQ 2d 1461 (1996)

[9] Phillips v. AWH Corporation, 415 F. 3d 1303, 1317, 75 USPQ 2d 1321, 1329 (Fed. Cir. 1995), *cert. denied*, 126 S. Ct. 1332 (2006)

The functional features of the claims are clear.

The functional limitations of reduced toxicity and enhancement of immune response are provided to further distinguish the claimed mutant CT from mutant CTs which do not have such bioactivity. The specification demonstrates assays by which one can determine and define the meaning of "reduced toxicity" required by the claim, such as the Y-1 Adrenal Cell assay of Example 3 and the ADP-ribosyltransferase assay of Example 5. These examples as well as the plain meaning of the claim language serve to indicate that the CT has reduced toxicity compared to wt CT. Similarly, the functional requirement for enhancement of immune response is defined and supported by the assays of Example 6, wherein the CT is assessed for its ability to enhance the immune response of an antigen. Thus the meaning of the functional requirements is also clear to one of skill in the art.

Thus, the pending claims of Appellants' invention are clear in their meaning and require no more than ordinary skill in, and knowledge of, the art to understand.

Miscellaneous Comments Responsive to the Examiner's Rejections

The following comments are a *bona fide* effort to address the specific comments addressed by the Examiner under this section. The comments above are believed to address the Examiner's concerns about functional characteristics, the amino acid at position 29, and the number of mutations, as well as upper limits of mutations. These issues do not make unclear the claim language requiring that a mutant CT carry the specific mutation in order to meet the claim limitations.

The Examiner also alleged that "[t]he mutants evidenced changes in the amino acid sequence of the holotoxin, what the changes were, were not specifically described, nor defined"[10] and pointed[11] to the following passage in the Appellants' specification (pages 44-45):

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[10] Page 5, point 14 of the Office Action dated May 26, 2006

[11] Page 6, lines 8-20 of Office Action , dated November 15, 2005

> "Furthermore, the regions encoding the ctxA and ctxB signal sequences were replaced with the signal sequence-encoding region of E. coli LT (LTIIb-B leader) in order to promote secretion of CT-CRME29R. The plasmid pIIB29H was then modified in an attempt to increase the expression of CT-CRME29H. The resulting plasmid, designated pPX2492, contained synthetic Shine Dalgarno sequences upstream of each of ctxA and ctxB. The two genes are genetically separated in pPX2492, unlike in V. cholerae, where the genes overlap. The two genes also have the LTIIb-B leader sequence upstream of each.

Appellants fail to see the relevance of this passage to the outstanding 35 USC § 112, second paragraph, rejection and specifically how it contradicts the clarity of the pending claims. Regardless of the leader sequence, the chimeric or wild-type nature of the mutant CT, if a protein is a mutant CT and if it contains an amino acid other than Asp replacing the deleted native Glu29, and has the functional attributes of the claims, it falls within the scope of the claims. This is clear regardless of the process used to delete the wt Glu29 and replace it with other than Asp. The pending claims, which are clear and explicit as required under this section. The fact that the specification contains descriptions of additional materials not presently claimed is irrelevant in the present determination.

Thus, the claims as presently pending are clear and unambiguous in meaning.

In view thereof, Appellants request reconsideration and withdrawal of these grounds for rejection.

(c) *Claims 1-2, 4, 6-8, 11, 13-17, 28, 30, 32-34, 38, and 39-43 are rejected under 35 USC § 102(b) over Rappuoli et al. (International Patent Publication No. WO 95/17211) as allegedly evidenced by Zhang et al. (J. Mol. Biol., 251: 564, 1994).*

Appellants respectfully request reconsideration and withdrawal of this rejection in view of following remarks.

As required under MPEP § 2131, "to anticipate a claim, the reference must teach every element of the claim". Note that "the reference" referred to in this

rejection is Rappuoli, as Zhang is only relied upon by the Examiner for providing the sequences, and comparison thereof, of wild-type cholera toxin (CT) and wild-type *E. coli* heat labile toxin (LT) in Figure 1 of page 564. Appellants do not dispute this point. In fact, Zhang further supports Appellants' assertion that all known CT sequences have a Glu at wild type position 29 by illustrating that position 29 of each toxin described in Zhang has a Glu at that position.

Nowhere in Rappuoli is there any reference to a mutant cholera holotoxin subunit A where the naturally-occurring Glu that occurs at wild-type CT-A position 29 of the mature peptide is deleted and is replaced with another amino acid. Rappuoli refers to immunogenic compositions containing an immunologically effective amount of an antigen and a mucosal adjuvant. Rappuoli's adjuvant is described as specifically having an amino acid ***substitution*** at position 7 of *E. coli* toxin (LT)[12], and describes generically a deletion at an unspecified amino acid position.[13] No specific mutations of CT were taught.

Nowhere in Rappuoli is there any reference to a mutant cholera holotoxin subunit A where the naturally-occurring Glu that occurs at wild-type CT-A position 29 is substituted, i.e., replaced with another amino acid. The specification of the present application clearly requires that the naturally occurring Glu at wild-type position 29 be replaced, not simply moved to a different position in the sequence by virtue of an amino acid deletion of any of the amino acid residues in wild-type positions 1-28. Therefore, the Glu at position 29 is no longer present in the claimed mutant cholera holotoxin sequence. Nor is the Glu at position 29 in the wild-type sequence located at positions 28 or 30, among other positions, of the mutant cholera holotoxin sequence. Consequently, Rappuoli's specific amino acid ***substitution*** at position 7 of LT, or Rappuoli's ***generic*** disclosure of a deletion at an unspecified

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[12] "For example, a mutant LT in accordance with the invention may possess an Arg7 to Lys7 **substitution** at position 7 of the A subunit, the so-called LTK7 mutant." (Rappuoli at page 6, lines 2-4; emphasis added)

[13] See, Rappuoli at page 5, lines 35-38, and page 7, lines 25-28

amino acid position, in combination with the teachings of Zhang results in a mutant LT that is entirely different than the mutant cholera holotoxin of Appellants' invention.

Therefore, Rappuoli alone or taken with Zhang does not anticipate the claims of the present invention.

In view of the above remarks, this rejection should be properly withdrawn.

(d) *Claims 1, 2, and 13 are rejected under 35 USC § 102(b) over Glineur et al. (Infection and Immunity, 62(10):4176, 1994).*

The Examiner asserted that Glineur discloses an antigenic composition that comprises a mutant holotoxin of cholera toxin with a tyrosine substituted at position 29.

Appellants respectfully request reconsideration and withdrawal of this rejection in view of the following remarks.

As required by MPEP § 2131, in order for Glineur to be a proper 35 USC § 102(b) reference, Glineur must teach every element of the claims. Glineur does not anticipate the claims of the present invention because Glineur does not teach an antigenic composition in which a mutant cholera holotoxin is used as an adjuvant for another antigen. Glineur does not anticipate the claims of the present invention because Glineur does not teach the mutant cholera holotoxin described in Appellants' claims.

Glineur Does Not Teach the Mutant Cholera Holotoxin Mutant Described in Appellants' Claims

Glineur's teachings related to cholera toxin mutants are limited to the deletion mutant E29Δ and the substitution mutant E29D. Glineur does not teach that the Glu at position 29 could be replaced with an amino acid other than Asp or that the same would provide a cholera toxin mutant with the properties necessary (including reduced toxicity) for use as an adjuvant in an antigenic composition. It is only

Appellants' disclosure that provides the teaching and support for successful use of an amino acid **substitution *other than Asp*** at position E29 to create a mutant cholera holotoxin useful as an adjuvant in an antigenic composition.

The Examiner asserted that Glineur discusses a mutant holotoxin that has tyrosine at amino acid position 29 and does not comprise either Glu or Asp at position 29 of the alpha subunit.[14] However, Glineur's deletion mutant is **not** the subject of Appellants' claims. For the reasons stated above with respect to Rappuoli, the **deletion** of any of the amino acids prior to the naturally-occurring Glu at wild-type CT-A position 29 would shift the specified wild-type Glu residue to another position in the sequence. However, Appellants' invention is not such a mutant. The pending claims of Appellants' invention require that the Glu at position 29 be deleted and an amino acid ***other than Asp*** be inserted in place thereof. Glineur in no way teaches this requirement of the pending claims. Thus, Glineur does not anticipate the invention of the amended claims.

Glineur Does Not Teach an Antigenic Composition in which a Mutant Cholera Holotoxin is used as an Adjuvant for Another Antigen

Glineur does not teach an antigenic composition which contains a first antigen and a mutant cholera holotoxin (CTX) that has an "adjuvant" effect on the first antigen. In fact, Glineur teaches away from the claimed invention, because of the statement that the E29D mutant "...had no significant effect on the ADP-ribosyltransferase activity".[15] Therefore, E29D would not be useful as an adjuvant, because it had the enzymatic activity of the wild-type CTX and thus likely the toxicity of the wild-type CTX as well.

Therefore, Glineur does not teach the antigenic composition provided by the present application.

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[14] Page 7, point 24 of Office Action dated May 25, 2006
[15] Page 4181, col. 2 and Table 1 of Glineur

In view of the above remarks, this rejection should be properly withdrawn.

CONCLUSION

Reversal of the examiner's rejection of the claims under appeal (claims 1-11, 13-17, 28-37, and 39-44) is requested.

Respectfully submitted,

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VIII. Claims Appendix

Claim 1(Previously Presented): An antigenic composition comprising

(a) at least one antigen from a pathogenic organism selected from the group consisting of a bacterium, a virus, a fungus and a parasite; and

(b) an effective adjuvanting amount of a mutant cholera holotoxin, wherein the mutant holotoxin has reduced toxicity compared to a wild-type cholera holotoxin, and has an amino acid which replaces the deleted glutamic acid which naturally occurs at position 29 of the mature A subunit of the wild-type cholera holotoxin, wherein said amino acid is other than aspartic acid, and wherein said mutant holotoxin enhances the immune response in a vertebrate host to said antigen.

Claim 2 (Previously Presented): The antigenic composition of Claim 1 wherein the antigenic composition comprises more than one antigen of (a).

Claim 3(Previously Presented): An antigenic composition comprising

(a) at least one antigen from a pathogenic organism selected from the group consisting of a bacterium, a virus, a fungus and a parasite; and

(b) an effective adjuvanting amount of a mutant cholera holotoxin, wherein the mutant holotoxin has reduced toxicity compared to wild-type cholera holotoxin, and has a histidine which replaces the glutamic acid which naturally occurs at position 29 of the A subunit of the wild-type cholera holotoxin and wherein said mutant holotoxin enhances the immune response in a vertebrate host to said antigen.

Claim 4(Previously Presented): The antigenic composition of Claim 1 wherein the antigen is selected from the group consisting of the *Haemophilus influenzae* P4 outer membrane protein, the *Haemophilus influenzae* P6 outer membrane protein, the *Haemophilus influenzae* adherence and penetration protein (Hap_s), the *Helicobacter pylori* urease protein, the *Neisseria meningitidis* Group B recombinant class 1 pilin

(rpilin), the *Neisseria meningitidis* Group B class 1 outer membrane protein (PorA), the respiratory syncytial virus fusion protein, a rotavirus virus-like particle and the herpes simplex virus (HSV) type 2 glycoprotein D (gD2).

Claim 5(Previously Presented): The antigenic composition of Claim 4 wherein the antigen is selected from the group consisting of the *Haemophilus influenzae* P4 outer membrane protein, the *Haemophilus influenzae* P6 outer membrane protein, the *Haemophilus influenzae* Hap_s protein, and any combination thereof.

Claim 6(Previously Presented): The antigenic composition of Claim 4 wherein the antigen is the *Helicobacter pylori* urease protein.

Claim 7(Previously Presented): The antigenic composition of Claim 4 the antigen is selected from the group consisting of the *Neisseria meningitidis* rpilin, *Neisseria meningitidis* PorA protein and any combination thereof.

Claim 8(Previously Presented): The antigenic composition of Claim 4 wherein the antigen is the respiratory syncytial virus fusion protein.

Claim 9(Previously Presented): The antigenic composition of Claim 4 wherein the antigen is a rotavirus virus-like particle.

Claim 10(Original): The antigenic composition of Claim 9 wherein the virus-like particle is a rotavirus 2/6-virus-like particle.

Claim 11(Previously Presented): The antigenic composition of Claim 4 wherein the antigen is HSV gD2.

Claim 12(Canceled)

Claim 13(Original): The antigenic composition of Claim 1 wherein the antigenic composition further comprises a diluent or carrier.

Claim 14(Original): The antigenic composition of Claim 1 which further comprises a second adjuvant in addition to the mutant cholera holotoxin.

Claim 15(Previously Presented): The antigenic composition of Claim 1, wherein at least one additional mutation is made to the A subunit of the mutant cholera holotoxin at a position other than said wild-type amino acid position 29.

Claim 16(Previously Presented): The antigenic composition of Claim 15 wherein the at least one additional mutation is made as a substitution for a naturally-occurring amino acid at an amino acid position of wild-type cholera holotoxin selected from the group consisting of the arginine at amino acid 7, the aspartic acid at position 9, the arginine at position 11, the histidine at position 44, the valine at position 53, the arginine at position 54, the serine at position 61, the serine at position 63, the histidine at position 70, the valine at position 97, the tyrosine at position 104, the proline at position 106, the histidine at position 107, the serine at position 109, the glutamic acid at position 100, the glutamic acid at position 112, the serine at position 114, the tryptophan at position 127, the arginine at position 146 and the arginine at position 192.

Claim 17(Previously Presented): A method for increasing the ability of an antigenic composition containing at least one antigen from a pathogenic organism selected from the group consisting of a bacterium, a virus, a fungus or a parasite to

elicit the immune response of a vertebrate host, which comprises administering to said host an antigenic composition of Claim 1.

Claims 18-27(Canceled)

Claim 28 (Previously Presented): The method of Claim 17 wherein the antigenic composition comprises more than one antigen.

Claim 29(Previously Presented): The method of Claim 17 wherein the amino acid substituted at wild-type position 29 is histidine.

Claim 30(Previously Presented): The method of Claim 17 wherein the antigen is selected from the group consisting of the *Haemophilus influenzae* P4 outer membrane protein, the *Haemophilus influenzae* P6 outer membrane protein, the *Haemophilus influenzae* Hap_s protein, the *Helicobacter pylori* urease protein, the *Neisseria meningitidis* rpilin, the *Neisseria meningitidis* PorA protein, the respiratory syncytial virus fusion protein, a rotavirus, virus-like particle and HSV gD2.

Claim 31(Previously Presented): The method of Claim 30 wherein at least one antigen is selected from the group consisting of the *Haemophilus influenzae* P4 outer membrane protein, the *Haemophilus influenzae* P6 outer membrane protein, the *Haemophilus influenzae* Hap_s protein, and any combination thereof.

Claim 32(Previously Presented): The method of Claim 30 wherein the antigen is the *Helicobacter pylori* urease protein.

Claim 33(Previously Presented): The method of Claim 30 wherein at least one antigen is selected from the group consisting of the *Neisseria meningitidis* rpilin, *Neisseria meningitidis* PorA protein and any combination thereof.

Claim 34(Previously Presented): The method of Claim 30 wherein the antigen is the respiratory syncytial virus fusion protein.

Claim 35(Previously Presented): The method of Claim 30 wherein the antigen is a rotavirus virus-like particle.

Claim 36(Original): The method of Claim 35 wherein the virus-like particle is a rotavirus 2/6-virus-like particle.

Claim 37(Previously Presented): The method of Claim 30 wherein the antigen is HSV gD2.

Claim 38(Canceled)

Claim 39(Original): The method of Claim 17 wherein the antigenic composition further comprises a diluent or carrier.

Claim 40(Original): The method of Claim 17 wherein the antigenic composition further comprises a second adjuvant in addition to the mutant cholera holotoxin.

Claim 41(Previously Presented): The method of Claim 17 wherein at least one additional mutation is made to the A subunit of the mutant cholera holotoxin at a position other than said wild-type amino acid position 29, wherein said mutant

holotoxin with said additional mutation enhances the immune response in a vertebrate host to said antigen.

Claim 42(Previously Presented): The method of Claim 41 wherein the at least one additional mutation is made as a substitution for a naturally-occurring amino acid of wild-type cholera holotoxin selected from the group consisting of the arginine at amino acid 7, the aspartic acid at position 9, the arginine at position 11, the histidine at position 44, the valine at position 53, the arginine at position 54, the serine at position 61, the serine at position 63, the histidine at position 70, the valine at position 97, the tyrosine at position 104, the proline at position 106, the histidine at position 107, the serine at position 109, the glutamic acid at position 100, the glutamic acid at position 112, the serine at position 114, the tryptophan at position 127, the arginine at position 146 and the arginine at position 192.

Claim 43(Previously Presented): A method of preparing an antigenic composition comprising combining

(a) at least one antigen from a pathogenic organism selected from the group consisting of a bacterium, a virus, a fungus and a parasite; and

(b) an effective adjuvanting amount of a mutant cholera holotoxin, wherein the mutant holotoxin has reduced toxicity compared to wild-type cholera holotoxin and has a substitution which replaces the glutamic acid which naturally occurs at position 29 of the A subunit of the wild-type cholera holotoxin with an amino acid other than aspartic acid, and wherein said mutant holotoxin enhances the immune response in a vertebrate host to said antigen.

Claim 44(Previously Presented): A method for increasing the ability of an antigenic composition containing at least one antigen from a pathogenic organism selected from the group consisting of a bacterium, a virus, a fungus or a parasite to

elicit the immune response of a vertebrate host, which comprises administering to said host an antigenic composition of Claim 3.

IX. Evidence Appendix

Exhibit A: Copy of Mekalanos et al., 1983, Nature, 306:551-557

This document was submitted by Appellants in the Information Disclosure Statement filed on October 3, 2001 and was entered by the Examiner on March, 2004.

Exhibit B: Copy of International Patent Application Publication No. WO 93/13202

This document was submitted by Appellants in the Information Disclosure Statement filed on October 3, 2001 and was entered by the Examiner on March, 2004.

Exhibit C: Copy of International Patent Application Publication No. WO 97/02348

This document was submitted by Appellants in the Information Disclosure Statement filed on October 3, 2001 and was entered by the Examiner on March, 2004. This document was also cited by the Examiner in the Office Action dated July 8, 2003.

Exhibit D: Copy of International Patent Application Publication No. WO 97/29771

This document was submitted by Appellants in the Information Disclosure Statement filed on October 3, 2001 and was entered by the Examiner on March, 2004. This document was also cited by the Examiner in the Office Action dated July 8, 2003.

Exhibit E: Copy of Vadheim K.L., et al., 1994, Microb. Pathog., 17(5):339-46

This document was cited by the Examiner in the Office Action dated July 8, 2003.

X. Related Proceedings Appendix

None